Issues in Genetic Testing: Real versus Not-so-Real

Roberta A Pagon, MD
Principal Investigator, GeneTests
Professor, Pediatrics
University of Washington
American Society of Human Genetics 2006 Annual Meeting

Single Gene Disorders

- Mutation in one gene alters the phenotype
- Identified by:
  - Phenotype alone
  - Biochemical genetic testing
    - Analyte
    - Enzyme
- Molecular genetic (DNA) testing

Uses of Molecular Genetic Testing

- **Medical care**
  - Diagnostic
  - Predictive with a treatment
- **Personal decision-making**
  - Predictive without a treatment
  - Carrier
  - Prenatal

Vignettes for the classroom

You are 20 years old

Vignette 1: Your father has just been diagnosed with familial adenomatous polyposis (FAP). What does this mean for you?

Vignette 2: Your mother has just been diagnosed with Huntington disease (HD). What does this mean for you?

- What is FAP?
- What causes it?
- What can I do about it?

- What is Huntington disease?
- What causes it?
- What can I do about it?

The place to go for information

www.genetests.org

Information resource for healthcare providers to help integrate genetic services into patient care

Located at
University of Washington
Seattle, WA

Funded by
National Institutes of Health

Funded by the
National Institutes of Health

GeneTests

10/03/06

359 *GeneReviews*
1,144 Clinics
608 Laboratories testing for
1,305 Diseases
1,010 Clinical
295 Research only

Administrative Use
(For Laboratory/Clinic Contacts, User Groups)

Welcome to the **GeneTests** Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the terms of use.

At This Site

- ***GeneReviews***
  Online publication of expert-authored disease reviews
- **Laboratory Directory** 
  International directory of genetic testing laboratories
- **Clinic Directory**
  International directory of genetics and prenatal diagnosis clinics
- **Educational Materials**
  - Illustrated glossary
  - About genetic services
  - PowerPoint® slide presentations

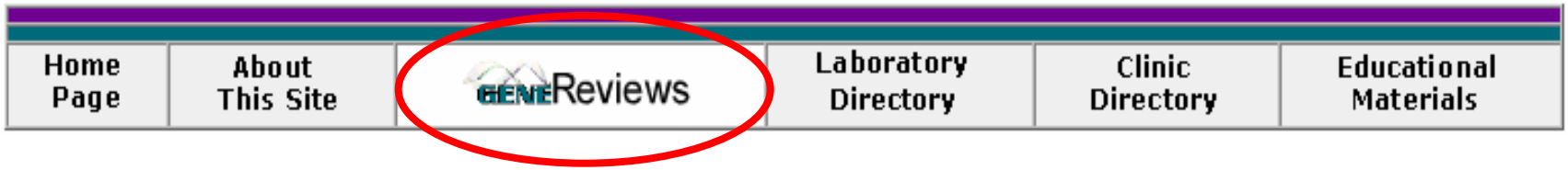
What's New

New Features
- **Carrier testing now included in laboratory search results**

New in *GeneReviews*

New Lab Listings
- **14 new listings**

Visit **GENETIC TOOLS** — Materials for teaching genetics in primary care settings



GeneReviews

- Genetic disease descriptions
- Current information on genetic test use in diagnosis, management, genetic counseling
- Expert-authored, peer-reviewed

GeneTests

Educational Materials

- Illustrated glossary
- Genetic counseling and testing primer
- PowerPoint™ presentations

GENEReviews
www.genetests.org

Huntington Disease

Genetic counseling. HD is inherited in an autosomal dominant manner. Offspring of an individual with a mutant allele have a 50% chance of inheriting the disease-causing allele. Predictive testing in asymptomatic adults at 50% risk is available, but requires careful thought, including pre-test and post-test counseling, as no treatment exists. Asymptomatic at-risk children should not have predictive testing. Although infrequently requested, prenatal testing by direct DNA testing is available for fetuses at 50% risk. Prenatal testing for fetuses at 25% risk can be performed using linkage analysis in such a way that the genetic status of the at-risk parent is not revealed.

---

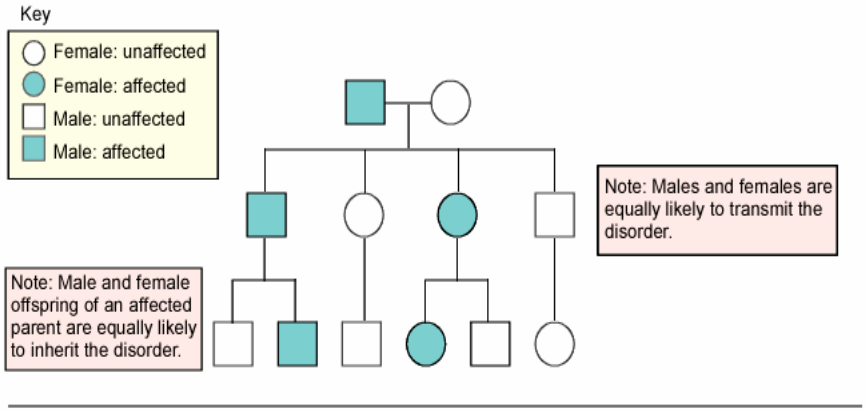
autosomal dominant: Describes a trait or disorder in which the phenotype is expressed in those who have inherited only one copy of a particular gene mutation (heterozygotes); specifically refers to a gene on one of the 22 pairs of autosomes (non-sex chromosomes)
Related Terms: de novo mutation; germline mosaicism; heterozygote; mode of inheritance; penetrance; variable expression

Learn More
Case Example
Full Glossary

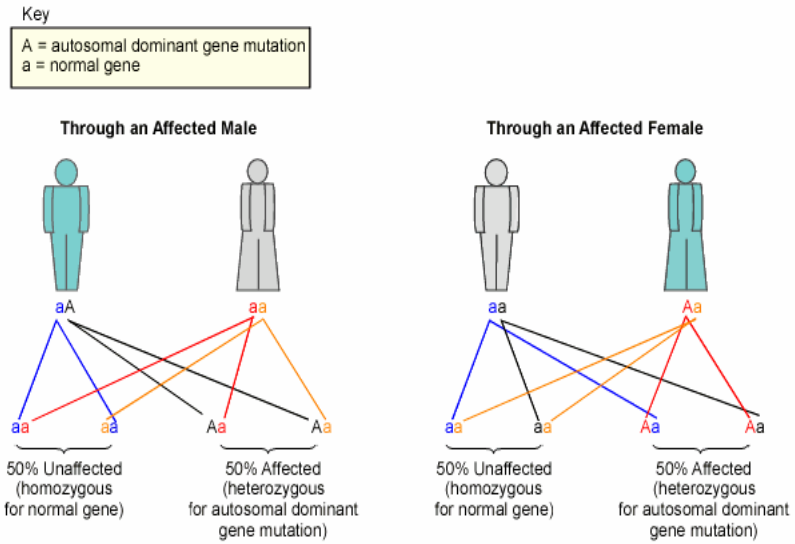
autosomal dominant: Describes a trait or disorder in which the phenotype is expressed in those who have inherited only one copy of a particular gene mutation (heterozygotes); specifically refers to a gene on one of the 22 pairs of autosomes (non-sex chromosomes)

Learn More

Pedigree Illustrating Autosomal Dominant Inheritance Pattern



Probability of Transmitting an Autosomal Dominant Mutation to Offspring



Posted: 10-1-02

Related Terms: de novo mutation; germline mosaicism; heterozygote; mode of inheritance; penetrance; variable expression

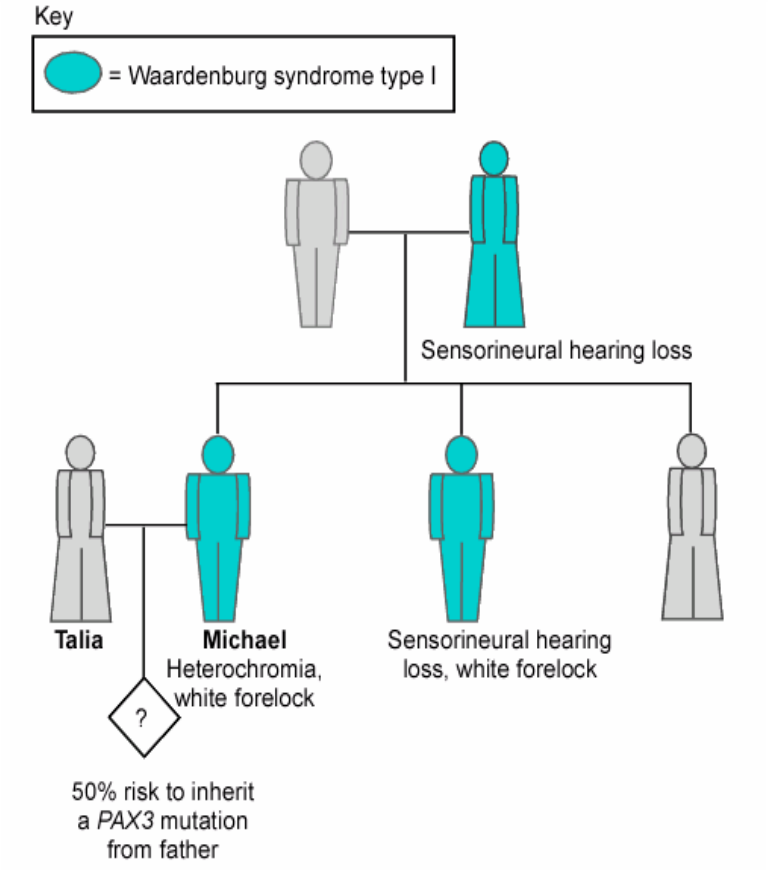
Case Example | Full Glossary | Instructions

GeneTests

Case Example

Case Example (autosomal dominant): Waardenburg syndrome type I

Talia and her husband, Michael, are seen for genetic counseling to discuss recurrence risks for a future pregnancy given Michael's family history of hearing loss. Michael himself has normal hearing but his mother and brother are deaf. It is noted that Michael has heterochromia of the eyes (eyes of different color). The genetic counselor inquires about pigmentation changes in other family members. Michael states that his brother has a patch of white hair just at the top of his forehead and admits that he has a similar patch of white hair, which he has chosen to dye. The clinical findings in this family are suggestive of Waardenburg syndrome type I, an autosomal dominant condition, which includes sensorineural hearing loss; pigmentary changes of the skin, hair, and eyes; and lateral displacement of the inner canthi (dystopia canthorum). Later review of the brother's medical records confirms this diagnosis. Michael and Talia are counseled that although Michael himself has normal hearing, he does, in fact, have the (*PAX3*) gene mutation for Waardenburg syndrome type I and has a 50% chance of transmitting the mutation to any future offspring.



Some Clinical Implications

- Risk of transmission of an autosomal dominant gene mutation from parent to child is 50%, regardless of the gender of the parent or of the child.
- Male-to-male transmission is characteristic of an autosomal dominant (AD) disorder and helps distinguish AD disorders from X-linked disorders.
- Individuals within a family who have not inherited the autosomal dominant gene mutation are at no greater risk than the background population of having a child with the condition (by *de novo* mutation).
- Reduced penetrance and variable expressivity occur frequently in autosomal dominant disorders.
- Autosomal dominant conditions are often seen in multiple generations.
- Mothers and fathers are equally likely to transmit or inherit the disorder.
- Sons and daughters of an affected parent are equally likely to inherit and transmit the disorder.

- What is FAP?
- What causes it?
- What can I do about it?

APC-Associated Polyposis Conditions

[Includes: Familial Adenomatous Polyposis, Gardner Syndrome, Turcot Syndrome, Attenuated FAP]

Authors: Cindy Solomon, MS
Randall W Burt, MD

Initial Posting: 18 December 1998
Last Update: 21 October 2005

Summary

Disease characteristics. *APC*-associated polyposis conditions include familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome. **FAP** is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop, beginning at a mean age of 16 years (range 7-36 years). By age 35 years, 95% of individuals with FAP have polyps; without colectomy, colon cancer is inevitable. The mean age of colon cancer diagnosis in untreated individuals is 39 years (range 34-43 years). Extracolonic manifestations are variably present and include polyps of the gastric fundus and duodenum, osteomas, dental anomalies, congenital hypertrophy of the retinal pigment epithelium (CHRPE), soft tissue tumors, desmoid tumors, and associated cancers. **Attenuated FAP** is characterized by a significant risk for colon cancer, but fewer colonic polyps (average of 30) than classic FAP, more proximally located polyps, and diagnosis of colon cancer at a later age; management may be substantially different. **Gardner syndrome** is characterized by colonic polyposis typical of FAP together with osteomas and soft tissue tumors. **Turcot syndrome** is the association of colonic polyposis and CNS tumors; the phenotypic features of Gardner syndrome and Turcot syndrome relate to the location of the *APC* mutation and are generally expressed in families with FAP.

Diagnosis/testing. *APC*-associated polyposis conditions are caused by mutations in the *APC* gene. The diagnosis of *APC*-associated polyposis conditions relies primarily upon clinical findings. Molecular genetic testing of *APC* detects disease-causing mutations in up to 95% of probands

APC-Associated Polyposis Conditions

GeneReviews

Summary

Disease description

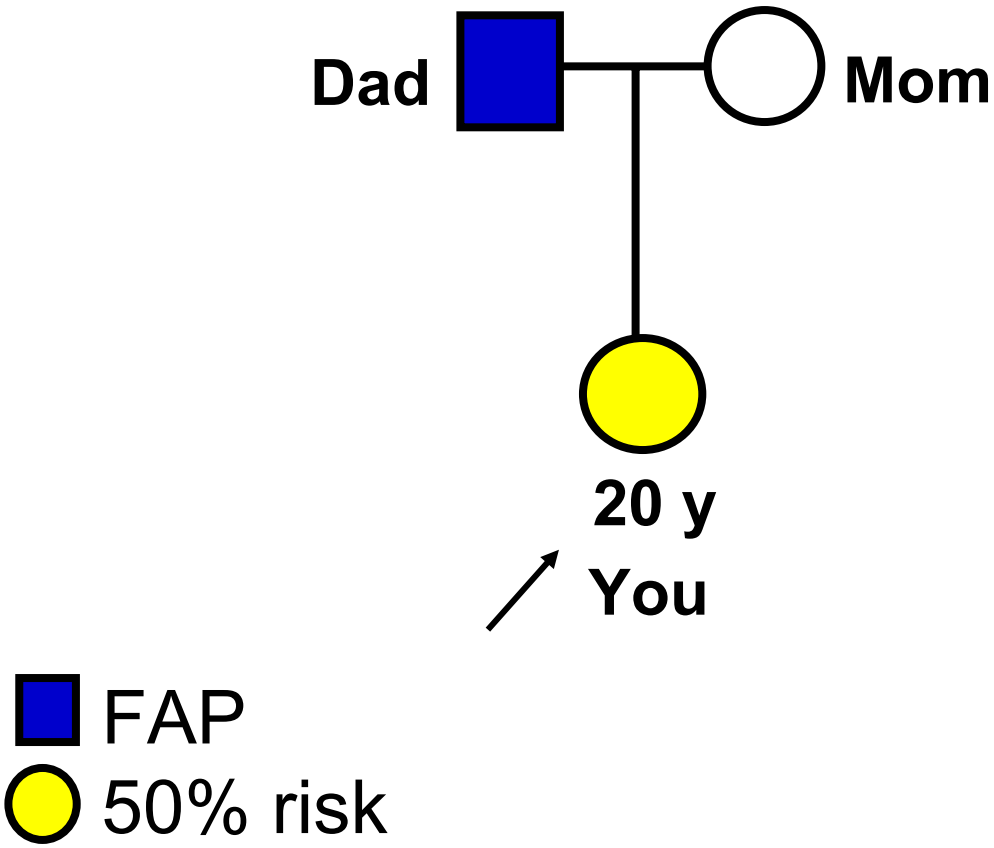
- Colon cancer syndrome
- Polyps (precancerous growths) develop 7-36 years
- Colon cancer at 34-43 years

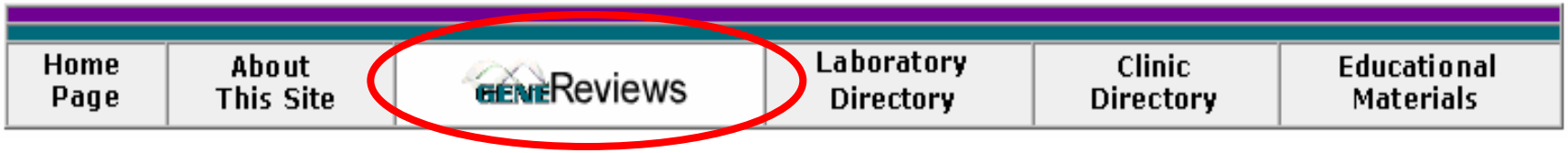
Diagnosis/testing

- 95% of patients have a mutation in *APC* gene

Genetic counseling

- **Mode of inheritance:** Autosomal dominant





APC-Associated Polyposis Conditions

GENEReviews

Management

Molecular genetic testing: By 10-12 years of age.

Surveillance:

- **Persons with an *APC* mutation**
  - Annual sigmoidoscopy beginning at age 12 years.
  - Colectomy (removal of the colon) when polyps appear.

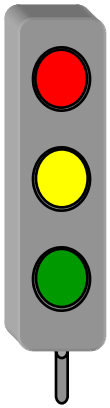
- **Persons without an *APC* mutation**
  - Routine colon cancer screening at age 50 years

GENETests

Uses of Molecular Genetic Testing

- **Medical care**
  - Diagnostic
  - Predictive with a treatment
- **Personal decision-making**
  - Predictive without a treatment
  - Carrier
  - Prenatal

Testing Strategy for FAP



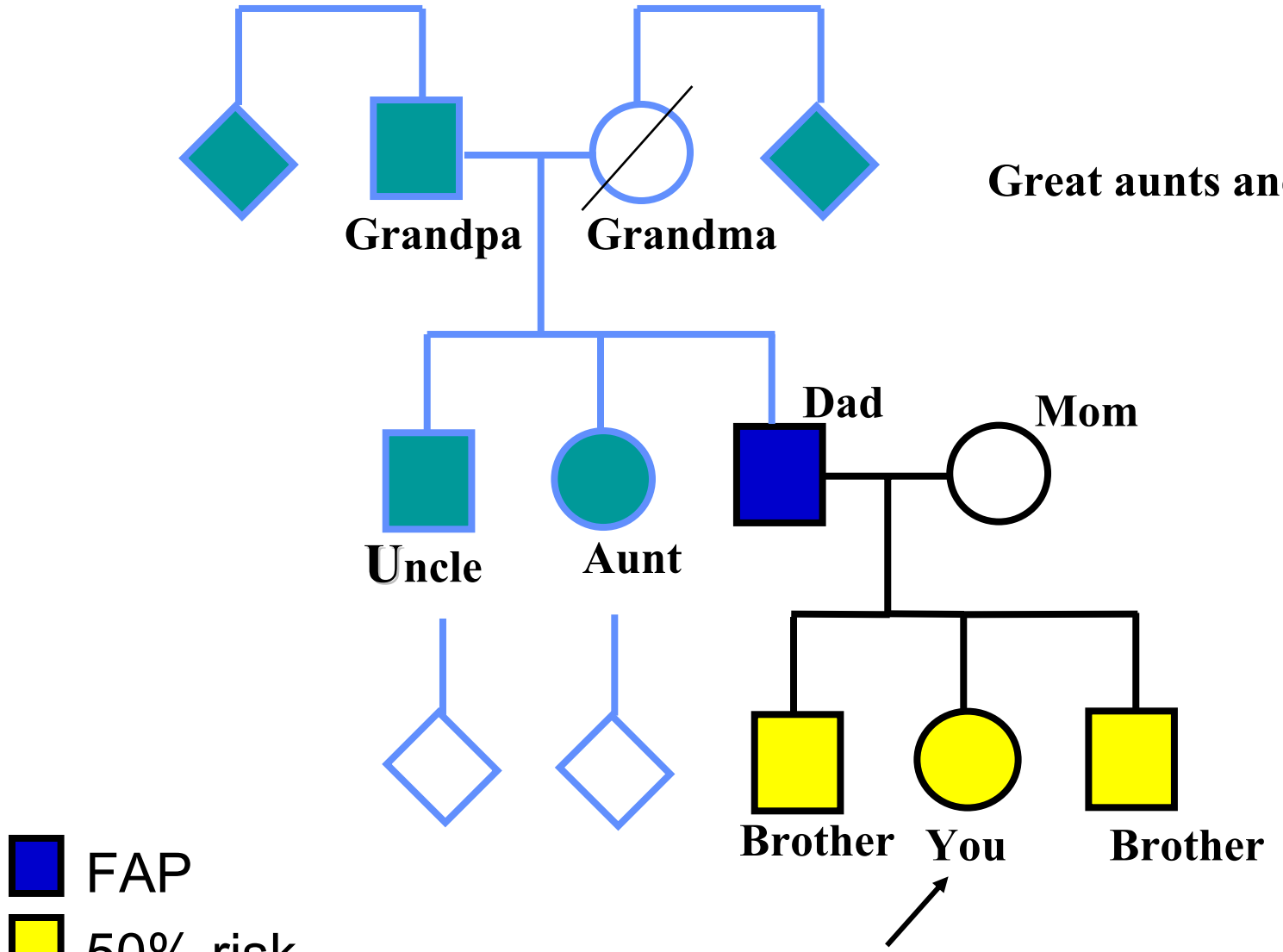
Test Dad

Mutation detected
- Direct testing useful
- Proceed with testing family

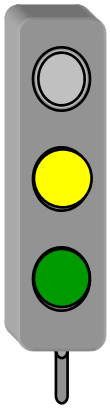
No mutation detected
- Direct testing not useful
- Do not proceed with testing family

Testing Strategy = Science Lesson

- Most genes have 100s of disease-causing mutations
- Genes have benign sequence variants (polymorphisms) which have no effect on health
- Sometimes it is unclear whether a sequence variant is disease-causing or benign
- The disease-causing mutation must be known before relatives at-risk can be tested
- Genetic tests usually cannot detect all disease-causing mutations in a gene
- Disease-causing mutations "run true" in families


Great aunts and uncles
Grandpa
Grandma
Uncle
Aunt
Dad
Mom
Brother
You
Brother
FAP
50% risk
Indeterminant risk

Testing and Genetic Counseling Strategy

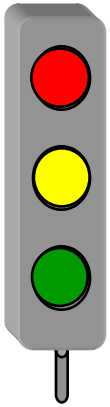


Test Dad

Mutation detected

- Direct testing useful
- Proceed with
  - Genetic counseling
  - Genetic testing of all at-risk relatives
  - Surveillance of mutation-positive relatives only

Testing and Genetic Counseling Strategy



Test Dad

No mutation detected STOP

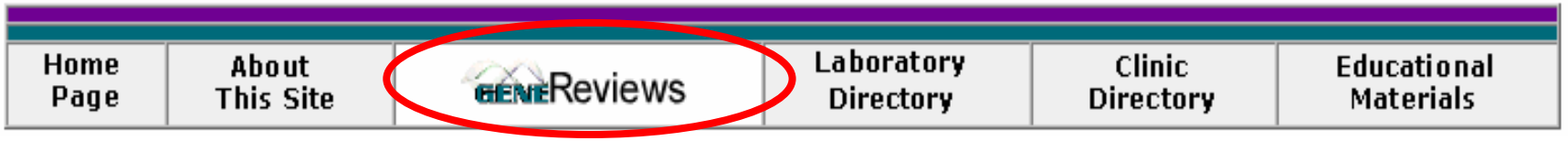
- Direct testing not useful

- Proceed with
  - Genetic counseling
  - Surveillance of at-risk relatives

Ethics Lesson

- Diagnosis of a genetic disorder has implications for many family members.
- Use of genetic testing has implications for many family members

- What is Huntington disease?
- What causes it?
- What can I do about it?



Huntington Disease

GENEReviews

Summary

Disease description

- Progressive motor, cognitive, and psychiatric disturbances
- Onset: 35 – 44 years
- Death: 15 – 18 years later

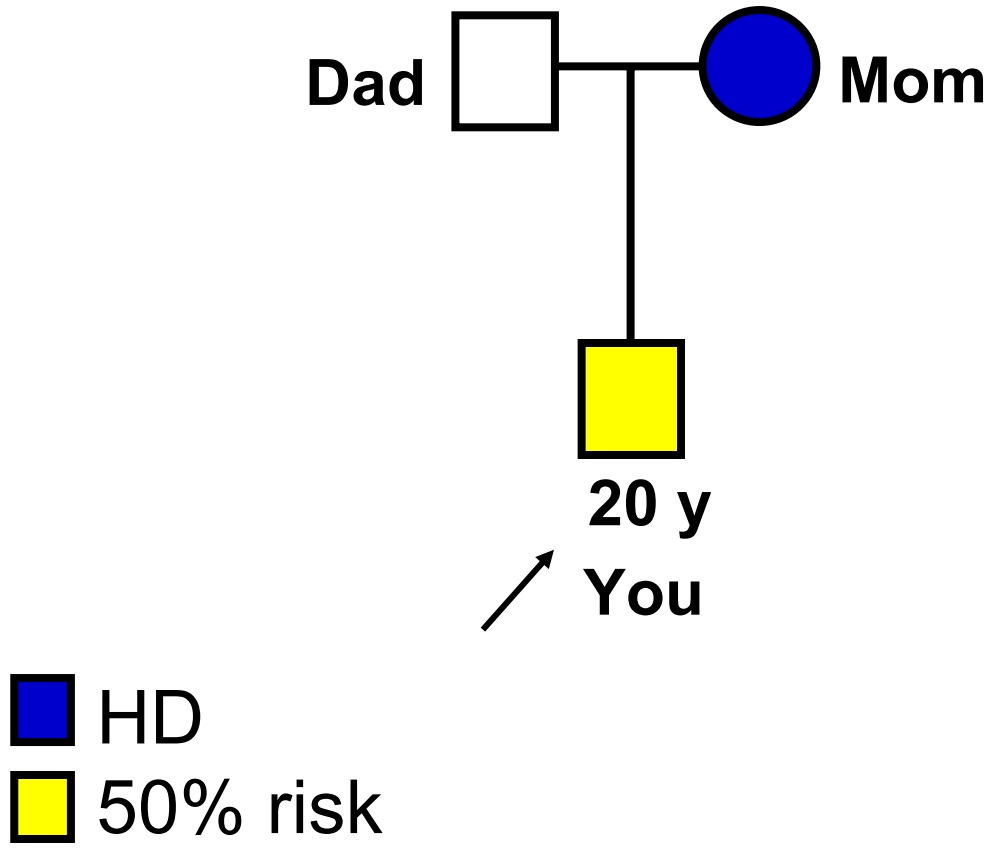
Diagnosis/testing

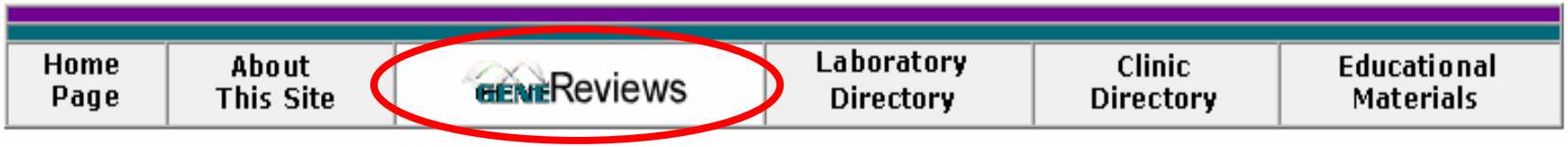
- 100% of patients have a mutation in *HD* gene

Genetic counseling

- **Mode of inheritance:** Autosomal dominant

GENETests





GENEReviews

Huntington Disease

Management

- No cure
- Supportive medical care (e.g., nutrition, comfort)
- Psycho-social support for family

GENETests

Uses of Molecular Genetic Testing

- **Medical care**
  - Diagnostic
  - Predictive with a treatment
- **Personal decision-making**
  - Predictive without a treatment
  - Carrier
  - Prenatal

Ethics Lesson

Why do predictive testing when no cure exists?

Personal decision-making

- Education
- Employment
- Life experiences
- Family planning

When: ≥ age 18 years

- Informed decision

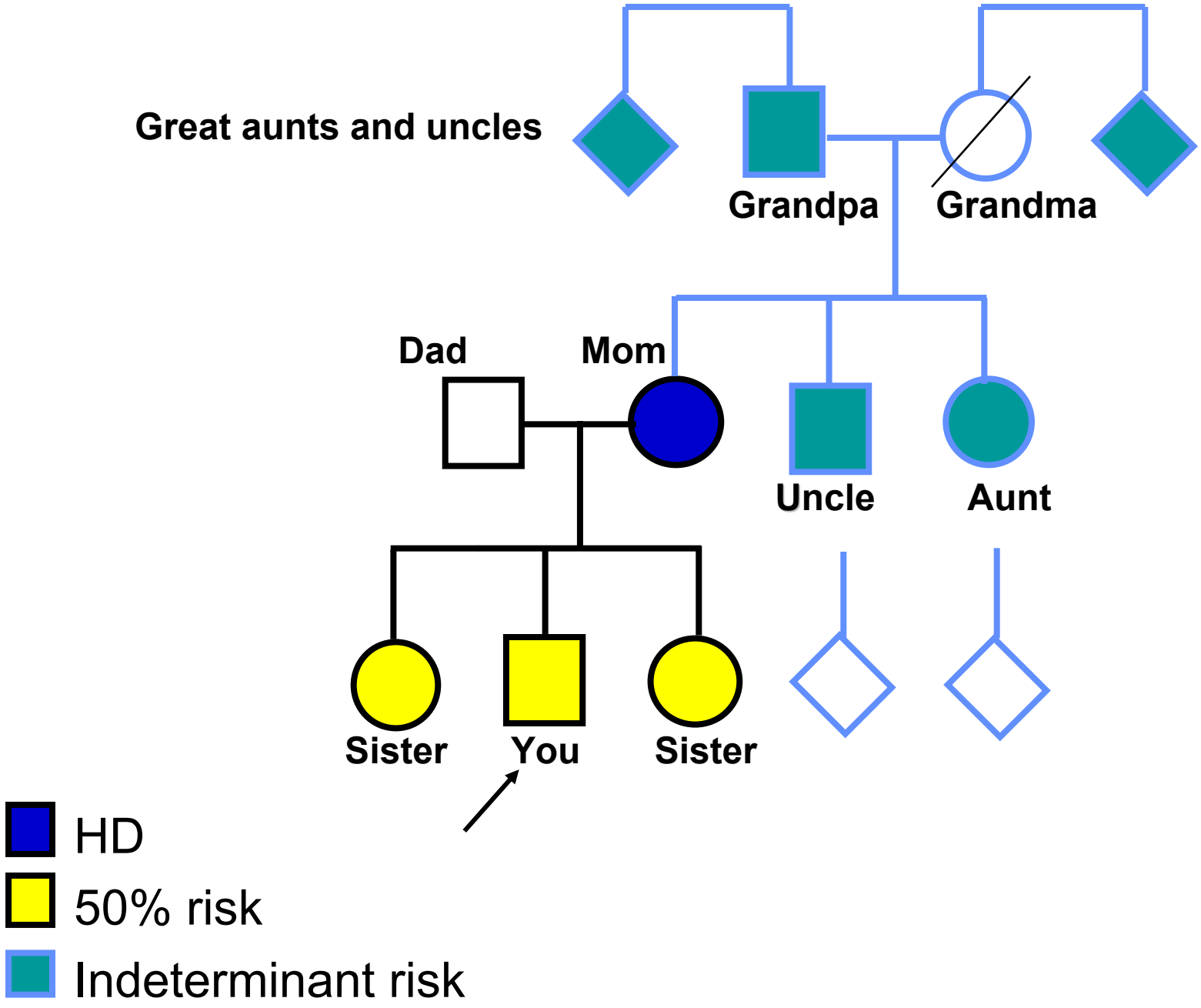
Why not test children who are < age 18 years?

- Social stigma (family, education, relationships)
- Deprives individual of the right to choose to know versus not know

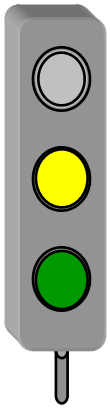
Testing Strategy = Science Lesson

Many inherited conditions mimic each other; therefore, the diagnosis must be secure before predictive testing is used.

Conclusion: Must confirm the diagnosis in an affected relative first


Great aunts and uncles
Grandpa
Grandma
Dad
Mom
Uncle
Aunt
Sister
You
Sister
HD
50% risk
Indeterminant risk

Testing and Genetic Counseling Strategy

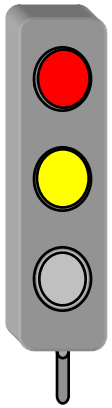


Test Mom

Mutation detected

- Direct testing useful
- Proceed with
  - Genetic counseling
  - Genetic testing of at-risk adult relati
    who choose to be tested

Testing and Genetic Counseling Strategy



Test Mom

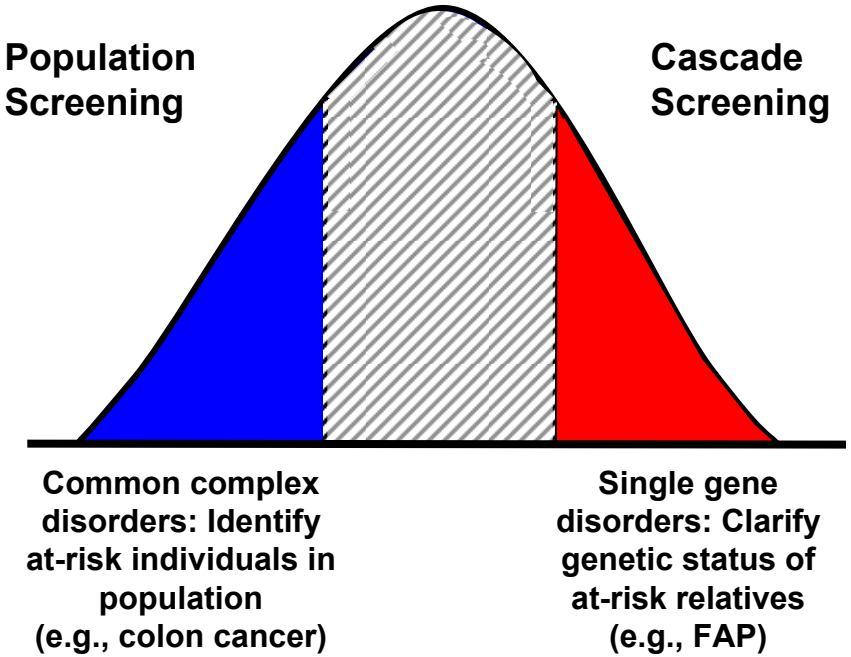
No mutation detected STOP

- **Diagnosis not known**

Direct to Consumer Testing

- What is the disorder for which the test is being used?
- What is the test?
- What evidence links the test to the disorder?
- How is the disorder usually diagnosed?
- What are the implications of a positive test result vs a negative test result on medical management? Personal decision-making? Risks to other family members?
- Who is going to help explain the results to all the family members who need to know?

“Personalized Medicine”



“Personalized Medicine”

Population screening to identify genetic predisposing risk factors in order to reduce the risk by changing: ? diet, ?behavior, ?life style, ?environmental exposures ?medications.

Vignette: You are a 40 yo biology professor. Your primary care doctor does a “colon cancer” test to define your risk of colon cancer. What are you going to do differently?

Issues in Genetic Testing: Real versus Not-so-Real